

## REMARKS

Claims 1-14 and 16-19 are pending in this application. Applicants have canceled claim 15 and added claim 19. Applicants have amended claims 1, 4, 13, 16, 17, and 18 to correct informalities and more clearly delineate the claimed subject matter. Applicants have amended claim 1 to substitute the term "repairing" with "insertion into." Support for this amendment can be found in the specification, e.g., on page 13, lines 22-23, and on page 14, lines 3-4. Applicants also amended claim 4 to replace the trade name "PLURONICS™" with the generic name of the compositions to which it refers. Support for the amendment to claim 4 can be found in the specification, e.g., on page 8, lines 5-7. In claim 13, the previously used abbreviation "CAD/CAM" was replaced by its definition "computer-aided design/computer-aided manufacturing," which is commonly used and known in the art. Claim 16 was amended to remove the term "injection-molded." Support for this amendment can be found in the specification, e.g., on page 15, line 16. Claim 17 was amended to include the phrase "prepared from a material." Support for this amendment can be found in the specification on page 8, lines 3-9. Claim 18 was amended to delete the phrase "and other cells that form cartilage," as being superfluous. Support for new claim 19 can be found in claim 16 and in the specification, e.g., on page 15, line 16.

Applicants have also capitalized the trademark PLURONICS™ on page 2, line 18, of the specification and have defined the term "CAD/CAM" as "computer-aided design/computer aided-manufacturing" on page 2, line 24. Note that "CAD" is defined on page 5, line 28, and "CAM" is defined on page 6, line 22, of the specification.

The claim amendments and revisions to the specification add no new matter. Reconsideration of the application as amended, is requested in view of the following remarks.

### 35 U.S.C. § 112, Second Paragraph

Claims 4, 13, 16, 17, and 18 have been rejected as being allegedly indefinite.

The Office Action states that the term "pluronic," used in claim 4, encompasses various different materials. Claim 4 has been amended to use the term "poly(oxyethylene)-

poly(oxypropylene) block polymers solidified by changes in temperature,” which is described in the application at page 8, lines 5-7.

The Office Action states that the meaning of the term “CAD/CAM,” as used in claim 13 is uncertain. Applicants respectfully disagree, but have amended claim 13 to define the term “CAD/CAM” as “computer-aided design/computer-aided manufacturing,” which is the well-known definition of the acronym and is used as such in the specification.

The Office Action also states that the meaning of “rapid prototyping” is uncertain. Applicants submit that the term “rapid prototyping” is an art-accepted term encompassing several techniques for generating a model of an object of interest (e.g., stereolithography) and would be understood by one of ordinary skill in the art. For a definition, see McGraw Hill Dictionary of Scientific Terms (6<sup>th</sup> ed. 2003), the relevant pages of which are attached as Exhibit 1.

The Office Action states that Claim 16 is confusing and unclear by not having antecedent basis for “injection-molded.” Claim 16 has been amended to remove the term “injection-molded.”

The Office Action states that claim 17 would be clarified by adding the phrase “prepared from a material” after “is” in line 1 of claim 17. Applicants submit that this phrase does not change the scope of the claim, but have added this phrase in the interest of moving the application towards allowance.

The Office Action states that the term “other cells that form cartilage” is uncertain with respect to cells that form and do not form cartilage. Applicants have deleted the above phrase.

Applicants submit that the amendments and arguments described above overcome all of the stated rejections under 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal thereof.

### **35 U.S.C. § 103(a)**

Claims 1-12 and 14-18 have been rejected as being allegedly unpatentable over Scholz (U.S. Pat No. 5,141,747) in view of Purchio et al (U.S. Pat No. 5,919,702) and Vacanti et al

(U.S. Pat No. 6,171,610 B1) taken with Neeffe (U.S. Pat No. 4,659,524), and if necessary in further view of Samuelsen (U.S. Pat No. 6,051,249). Claim 13 has been rejected as being allegedly unpatentable over the references as applied to claims 1-12 and 14-18 and further in view of Abbott et al. (1998).

According to the Office Action (at page 6, lines 4-12):

It would have been obvious to substitute for the collagen membrane used by Scholz for tympanic membrane repair, tympanic membrane tissue produced by adding cells to a hydrogel solution followed by adding the solution to a mold of a desired shape, and gelling the hydrogel and culturing the cells as suggested by Purchio et al and Vacanti et al since the tissue produced in this manner would have been expected to provide the function of the collagen membrane and be superior to the collagen membrane by being more similar to tympanic membrane tissue.

Applicants respectfully traverse this rejection with regard to the presently pending claims. The present invention is directed to methods of making and using a living tissue construct for repairing a perforation in a tympanic membrane. Scholz discloses the manufacture and use of an artificial membrane, made of denatured and sterilized collagen, to repair tympanic membrane. Purchio et al. and Vacanti et al. are directed, generally, to methods for generating new tissues from hydrogel-cell compositions, in vitro, and to methods for their use in transplantation. More specifically, Purchio et al. is directed to the production of cartilage tissue in vitro and therapeutic applications including hip prostheses, knee reconstruction, replacement of joint cartilage, and cosmetic reconstruction.

The MPEP states, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (MPEP § 2143.01).

Nowhere does Scholz disclose or suggest the use of living tissue in a method for repairing a perforation in a tympanic membrane. Moreover, there is no suggestion, in either Purchio et al. or Vacanti et al. to use tissues generated in vitro specifically to repair a perforation in a tympanic membrane as recited in the present claims. In stating that it would have been obvious to "...substitute for the collagen membrane used by Scholz for tympanic membrane

repair, tympanic membrane tissue produced by adding cells to a hydrogel solution... ” the Examiner is improperly ascribing specific attributes to the tissue generated by the methods of Purchio et al. or Vacanti et al., since neither of these references discloses or suggests methods of making “tympanic membrane tissue.” There is nothing in the cited references to suggest the substitution of tympanic membrane tissue with living cells for the collagen membrane of Scholz, as would be required to establish a prima facie case of obviousness. In fact, the proposed substitution completely eviscerates the inventive composition of Scholz, leaving only a method of use.

Scholz states, “...heated collagen molecules are cast into a desired shape, such as a film, and then allowed to cool and gel... After cooling, the interpenetrating, denatured collagen molecules are cross-linked to form an artificial membrane useful in tympanic membrane repair... Preferably the gel is dehydrated, which is believed to cause some cross-linking of the collagen molecules” (col. 2, lines 27-39). Scholz states further that “[p]referably, after dehydration the molecules are further cross-linked to increase the burst strength of the membrane. Further cross-linking is preferably performed by treating the membrane with chemical cross-linking agents or exposing the membrane to sufficient actinic radiation” (col. 2, lines 42-47). “For example, the membrane is immersed in succinyl chloride, either neat or in pyridine or other suitable organic base that would neutralize HCl evolved during the cross-linking reaction... ” (col. 2, lines 54-59). In addition, Scholz notes, “[u]seful forms of actinic radiation include ultraviolet light, gamma radiation, and electron beam radiation Sources [sic] and methods of applying radiation to the membrane will be apparent to the skilled artisan. After cross-linking, the membrane is preferably washed to remove unreacted agents, and further sterilized, e.g., by autoclaving or exposure to gamma radiation or ethylene oxide, before use in tympanic membrane repair” (col. 2, lines 66-68 and col. 3, lines 1-6).

It would be clear to one of skill in the art from a review of Scholz, that dehydration, cross-linking, and sterilization are utterly incompatible with and do not suggest in the least making a composition comprising live cells. To the contrary, they suggest that the non-biological composition described affords an adequate solution to the problem at hand. With

respect to extracting the method of use in Scholz (i.e., repairing a perforation in a tympanic membrane) and ignoring the composition upon which it is based, as demanded by the proposed substitution, the Federal Circuit Court has warned that “[e]ach prior art reference must be evaluated as an entirety, and...all of the prior art must be evaluated as whole” (*Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 (Fed. Cir. 1987)) and that “[o]ne cannot pick and choose among isolated disclosures in the prior art to deprecate the claimed invention” (*In re Fine*, 837 F.2d at 1075 (Fed. Cir. 1988)) and further that “[a] court may not, with 20-20 hindsight, utilize an inventor’s claims as a template and reconstruct his invention willy-nilly by picking and choosing elements at will from the prior art” (*Motorola, Inc. v. Interdigital Technology Corp.*, 930 F. Supp. 952, 974 (Fed. Cir. 1997)).

Applicants respectfully submit that it appears that the Examiner has used impermissible hindsight based on the present application to suggest the desirability of combining the teachings of the cited references. Even though the invention may seem simple on its face, it is certainly not obvious in view of the cited references.

Further references cited by the examiner including Neefe (U.S. Pat No. 4,659,524), Samuelsen (U.S. Pat No. 6,051,249), and Abbott et al. (1998) are directed, generally, to the design and use of negative molds. Although the present invention teaches the use of negative molds, none of these references alone or in combination, cure the deficiencies of the primary references of Scholz, Purchio et al., and Vacanti et al. Thus, claims 2-13 and 16-19, which depend from claim 1, are allowable for at least the same reasons as recited above.

Claim 14, which recites “[a] method of repairing a perforation in a tympanic membrane in a mammal,” is also allowable for at least the same reasons as cited above.

In light of the foregoing, applicants respectfully request that the rejection be withdrawn.

## CONCLUSION

Applicants respectfully request that all claims be allowed.

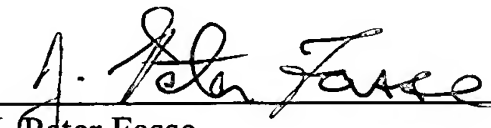
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Respectfully submitted,

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consisting of heat addition at constant pressure, isentropic expansion, heat rejection at constant pressure, and isentropic compression; used as an ideal standard for the performance of heat-engine and heat-pump installations operating with a condensable vapor as the working fluid, such as a steam power plant. Also known as steam cycle. { 'ræŋ-kən, sī-kəl }

**Rankine efficiency** [MECH ENG] The efficiency of an ideal engine operating on the Rankine cycle under specified conditions of steam temperature and pressure. { 'ræŋ-kən i, fish-ən-si }

**Rankine-Hugoniot equations** [THERMO] Equations, derived from the laws of conservation of mass, momentum, and energy, which relate the velocity of a shock wave and the pressure, density, and enthalpy of the transmitting fluid before and after the shock wave passes. { 'ræŋ-kən yū'gō-nē-ō i, hwi-zhənz }

**Rankine temperature scale** [THERMO] A scale of absolute temperature; the temperature in degrees Rankine (°R) is equal to 5/9 of the temperature in kelvins and to the temperature in degrees Fahrenheit plus 459.67. { 'ræŋ-kən 'təm-prə-cher-ə-skal }

**Rankine vortex** [FL MECH] A vortex with a vertical axis and circular motion, in which the motion is that of a rotating solid cylinder inside some fixed radius, and the circulation is constant outside this radius. { 'ræŋ-kən, vɔr, teks }

**Ranking method** [IND ENG] A system of job evaluation wherein each job as a whole is given a rank with respect to all the other jobs, and no attempt is made to establish a measure of value. { 'ræŋk-ɪŋ, meth-əd }

**rankinite** [MINERAL]  $\text{Ca}_3\text{Si}_2\text{O}_7$  A monoclinic mineral composed of calcium silicate. { 'ræŋ-kə-nīt }

**RANK ligand** [BIOCHEM] A local paracrine factor that originates from osteoblasts and mediates the effects of most, if not all, agents that are known to impact osteoclast development in bone. Also known as osteoprotegerin ligand. { 'ræŋk 'lɪg-ənd }

**rank of an observation** [STAT] The number assigned to an observation if a collection of observations is ordered from smallest to largest and each observation is given the number corresponding to its place in the order. { 'ræŋk əv ən 'æb-sərvə-shən }

**rank-order statistics** [STAT] Statistics computed from ranks of the observations rather than from the observations themselves. { 'ræŋk 'ɔr-dər stə'tis-tiks }

**rank tests** [STAT] Tests which use the ranks of observations with respect to one another rather than the observations themselves. { 'ræŋk, tests }

**Rankine oil-mining system** [PETRO ENG] A method used to get oil from oil sands that involves driving mine galleries from shafts communicating to the surface in impermeable strata above and below the oil strata; holes drilled at short intervals along the galleries into the oil sands drain the oil or gas through pipes sealed in the drill holes into tanks from which the gas or oil is pumped to the surface. { 'ræŋ-ē 'ɔɪl, mɪn-ɪŋ, sɪs-təm }

**Rankine well** [CIV ENG] A well that has a center caisson with horizontal perforated pipes extending radially into an aquifer; particularly applicable to the development of thin aquifers at shallow depths. { 'ræŋ-ē, wel }

**Ranque effect** [FL MECH] An effect whereby turbulent flow in a tube supplied with air through a tangential nozzle at high pressure produces warming near the walls of the tube and cooling at the axis. { 'ræŋk i, fekt }

**RANS analysis** See Reynolds-averaged Navier-Stokes analysis. { 'rænz ə, nəɪ-ə-səs }

**rankinite** [MINERAL]  $\text{Cu}(\text{Fe}, \text{Al})_2(\text{SO}_4)_4 \cdot 7\text{H}_2\text{O}$  A sky-blue mineral composed of hydrous copper iron aluminum sulfate. { 'ræŋ-sə, mīt }

**ranula** [MED] A retention cyst of a salivary gland. { 'ræŋ-yə-lə }

**Ranunculaceae** [BOT] A family of dicotyledonous herbs in the order Ranunculales distinguished by alternate leaves with net venation, two or more distinct carpels, and numerous stamens. { rə, nəŋ-kyə'lās-ē, ē }

**Ranunculales** [BOT] An order of dicotyledons in the subclass Magnoliidae characterized by its mostly separate carpels, triaperturate pollen, herbaceous or only secondarily woody habit, and frequently numerous stamens. { rə, nəŋ-kyə'lā-lēz }

**raob** See radiosonde observation. { 'rā, əb }

## EXHIBIT I:

## DEFINITION OF RAPID PROTOTYPING

**Raoult's law** [PHYS CHEM] The law that the vapor pressure of a solution equals the product of the vapor pressure of the pure solvent and the mole fraction of solvent. { rā'ulz, lō }

**rapakivi** [PETR] Granite or quartz monzonite characterized by orthoclase phenocrysts mantled with plagioclase. Also known as wiborgite. { 'rā-pə'kē-vē }

**rapakivi texture** [PETR] An igneous and metamorphic rock texture in which spherical potassium feldspar crystals are surrounded by a rim of sodium feldspar, both within a finer-grained matrix. { 'rā-pə'kē-vē 'teks-cher }

**rape** [BOT] *Brassica napus*. A plant of the cabbage family in the order Capparales; the plant does not form a compact head, the leaves are bluish-green, deeply lobed, and curled, and the small flowers produce black seeds; grown for forage. { rāp }

**rape oil** [MATER] A fatty, nondrying or semidrying, viscous, dark-brown to yellow oil with unpleasant taste and aroma, obtained from the seed of rape and turnip; soluble in ether, carbon disulfide, and chloroform; solidifies at -2 to -10°C; used to make lubricants and rubber substitutes, as an illuminant, and in steel heat treatment. Also known as colza oil; rape-seed oil. { 'rāp, ɔɪl }

**rape-seed oil** See rape oil. { 'rāp, sēd, ɔɪl }

**raphania** [MED] A disease thought to be due to chronic ingestion of the poison in seeds of the wild radish. { rə'fan-yə }

**raphe** [ANAT] A broad seamlike junction between two lateral halves of an organ or other body part. [BOT] 1. The part of the funiculus attached along its full length to the integument of an anatropous ovule, between the chalaza and the attachment to the placenta. 2. The longitudinal median line or slit on a diatom valve. { 'rā-fē }

**Raphidae** [VERT ZOO] A family of birds in the order Columbiformes that included the dodo (*Raphus calcullatus*); completely extirpated during the 17th and early 18th centuries. { 'raf-ə, dē }

**raphide** [BOT] One of the long, needle-shaped crystals, usually consisting of calcium oxalate, occurring as a metabolic by-product in certain plant cells. { 'rāf, id }

**rapid** [HYD] A portion of a stream in swift, disturbed motion, but without cascade or waterfall; usually used in the plural. { 'rap-əd }

**rapid access loop** [COMPUT SCI] A small section of storage, particularly in drum, tape, or disk storage units, which has much faster access than the remainder of the storage. { 'rap-əd 'æk, ses, lūp }

**rapid-curing asphalt** [MATER] A liquid asphalt composed of asphalt cement and a gasoline- or naphtha-type diluent. Abbreviated RC asphalt. { 'rap-əd 'kyūr-ɪŋ 'as, fɔlt }

**rapid-eye-movement sleep** [PSYCH] That part of the sleep cycle during which the eyes move rapidly, accompanied by a loss of muscle tone and a low-amplitude encephalogram recording; most dreaming occurs during this stage of sleep. Abbreviated REM sleep. { 'rap-əd 'ɪ, mʊv-mənt, slēp }

**rapid fire** [ORD] Rate of firing small arms or automatic weapons, faster than slow fire, but slower than quick fire. { 'rap-əd 'fɪr }

**rapid flow** [HYD] Water flow whose velocity exceeds the velocity of propagation of a long surface wave in still water. Also known as supercritical flow. { 'rap-əd 'flō }

**rapid memory** See rapid storage. { 'rap-əd 'mem-rē }

**rapid proton capture process** [ASTROPHYS] A mode of explosive nucleosynthesis in which each of the nuclei lighter than iron captures many protons, populating nuclides near the proton drip line, and these subsequently undergo a series of beta decays back to one of the stable nuclides. Also known as *rp*-process. { 'rap-id, prō, tən 'kap-cher, prā, ses }

**\*rapid prototyping** [IND ENG] A modeling process used in product design in which a CAD drawing of a part is processed to create a file of the part in slices, and then a part is built by depositing layer (slice) upon layer of material; includes stereolithography, selective laser sintering, or fused deposition modeling. { 'rap-əd 'prōd-ə, tɪp-ɪŋ }

**rapid quenching** [MET] Superfast cooling ( $1-5 \times 10^6$  K per second) of a molten metal to produce new and amorphous alloys and new crystalline material with improved properties. { 'rap-əd 'kwench-ɪŋ }

**rapid sand filter** [CIV ENG] A system for purifying water,

## RANUNCULACEAE



Colorado columbine (*Aquilegia coerulea*). (U. S. Forest Service photograph by C. A. Kulzleb)

On the cover: Representation of a fullerene molecule with a noble gas atom trapped inside. At the Permian-Triassic sedimentary boundary the noble gases helium and argon have been found trapped inside fullerenes. They exhibit isotope ratios quite similar to those found in meteorites, suggesting that a fireball meteorite or asteroid exploded when it hit the Earth, causing major changes in the environment. (Image copyright © Dr. Luann Becker. Reproduced with permission.)

Over the six editions of the Dictionary, material has been drawn from the following references: G. M. Garrity et al., *Taxonomic Outline of the Prokaryotes*, Release 2, Springer-Verlag, January 2002; D. W. Linzey, *Vertebrate Biology*, McGraw-Hill, 2001; J. A. Pechenik, *Biology of the Invertebrates*, 4th ed., McGraw-Hill, 2000; U.S. Air Force Glossary of Standardized Terms, AF Manual 11-1, vol. 1, 1972; F. Casey, ed., *Compilation of Terms in Information Sciences Technology*, Federal Council for Science and Technology, 1970; *Communications-Electronics Terminology*, AF Manual 11-1, vol. 3, 1970; P. W. Thrush, comp. and ed., *A Dictionary of Mining, Mineral, and Related Terms*, Bureau of Mines, 1968; A DOD Glossary of Mapping, Charting and Geodetic Terms, Department of Defense, 1967; J. M. Gilliland, *Solar-Terrestrial Physics: A Glossary of Terms and Abbreviations*, Royal Aircraft Establishment Technical Report 67158, 1967; W. H. Allen, ed., *Dictionary of Technical Terms for Aerospace Use*, National Aeronautics and Space Administration, 1965; *Glossary of Stinfo Terminology*, Office of Aerospace Research, U.S. Air Force, 1963; *Naval Dictionary of Electronic, Technical, and Imperative Terms*, Bureau of Naval Personnel, 1962; R. E. Huschke, *Glossary of Meteorology*, American Meteorological Society, 1959; *ADP Glossary*, Department of the Navy, NAVSO P-3097; *Glossary of Air Traffic Control Terms*, Federal Aviation Agency; *A Glossary of Range Terminology*, White Sands Missile Range, New Mexico, National Bureau of Standards, AD 467-424; *Nuclear Terms: A Glossary*, 2d ed., Atomic Energy Commission.

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